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ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/905,293	ROSOK ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-64* is/are pending in the application.

4a) Of the above claim(s) *23-27 and 32-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-22,28-31 and 53-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: 'Antibodies: General Information' (7 pages).

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 11/23/05 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 09/21/05 and 05/25/06 in response to the final Office Action mailed 03/21/05. Applicants have amended the claims and the specification.

Status of Claims

3) Claims 1-6 have been amended via the amendment filed 09/21/05.

New claims 51-64 have been added via the amendment filed 09/21/05.

Claims 1-6 and 8-64 are pending in the instant application.

Claims 1-6, 8-22, 28-31 and 53-64 are under examination.

Drawings

4) Acknowledgment is made of Applicants' submission of replacement drawings filed 03/09/06 for Figures 14A-14J, Figures 18A-18F, 19A-19N, and Figures 26-28.

Substitute Sequence Listing

5) Acknowledgment is made of Applicants' substitute sequence listing filed 05/25/06, which has been entered on 05/30/06.

Prior Citation of Title 35 Sections

6) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

7) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and

made of record.

Objection(s) Maintained

8) The objection to the drawings made in paragraph 6 of the Office Action mailed 08/14/02 and maintained in paragraph 7 of the Office Action mailed 06/02/04 and paragraph 5 of the Office Action mailed 03/21/05 is maintained for reasons set forth therein.

Objection(s) Withdrawn

9) The objection to the specification made in paragraph 7 of the Office Action mailed 03/21/05 is withdrawn in light of Applicants' amendment to the specification.

10) The objection to the specification made in paragraph 8 of the Office Action mailed 03/21/05 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

11) The rejection of claims 1-6 made in paragraph 13(d) of the Office Action mailed 06/02/04 and maintained in paragraph 19 of the Office Action mailed 03/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claims 1-6, 8-22 and 28-31 made in paragraph 20 of the Office Action mailed 03/21/05 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

13) The rejection of claims 1-6, 8-12, 15, 16, 19, 20 and 28-31 made in paragraph 21 of the Office Action mailed 03/21/05 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn. Upon further evaluation of the instant specification together with Applicants' arguments presented on pages 16-19 of Applicants' amendment filed 09/21/05, a new ground of rejection is set forth below.

Scope of the Invention

14) Lines 8-15 of page 10 of the instant specification provide the definition for 'multiple toxicity associated domains', which definition is reproduced below: [Emphasis added].

> As used herein the terms "multiple toxicity associated domains" means more than one discrete toxicity associated domain. As there appear to be at least two toxicity associated domains in the immunoglobulin molecule, one roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331,

> an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues in both of these domains. **This definition excludes structural alterations targeting a single toxicity associated domain.**

Applicants have previously emphasized this exclusive definition on page 6 of their amendment filed 06/14/1999 and page 5 of the Appeal Brief filed 03/13/01 by stating the following Emphasis added]:

> By utilizing antibodies which have alterations **both** in a toxicity associated domain in the C-terminal region of the CH2 domain (roughly localized to amino acids 310-331) **as well as** alterations in a toxicity associated domain in the N-terminal region of the CH2 domain (roughly localized to amino acids 231-238), Applicants provide a means of significantly inhibiting immunoglobulin-induced toxicity.

This definition clearly excludes the use in the claimed method of hBR96-2B antibody having alterations only at amino acids 235 and 236; hBR96-2C antibody having alterations only at amino acids 318, 320 and 322; hBR96-2D antibody having alterations only at amino acid residue 331; and hBR96-2G antibody having alterations only at amino acid residues 318, 320, 322 and 331. Yet these antibodies or their fusion proteins are encompassed in the scope of the claims, for example, claims 53, 54, 59, 60, 64 and 63.

Rejection(s) Maintained

15) The rejection of claim 1 made in paragraph 13(b) and the rejection of claims 2-6 made in paragraph 13(c) of the Office Action mailed 06/02/04 and maintained in paragraph 18 of the Office Action mailed 03/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants submit that one skilled in the art of immunology would know how to number the amino acids in the CH_2 domain and thus would be able to locate the appropriate amino acids in a generic immunoglobulin. The instant specification at lines 27-29 of page 21 teaches that the system of amino acid position numbering is found in Kabat *et al.* Sequences of Proteins of Immunological Interest. 5th Edn., 1991.

Applicants' argument has been carefully considered, but is not persuasive. Instant claims, as amended, recite that the administered immunoglobulin is modified by structurally altering multiple toxicity-associated regions, which 'are localized to' amino acids 231-238 and 310-331 of the CH_2 domain of 'an immunoglobulin'. The disclosure at lines 10 and 11 of page 10 of the instant specification vaguely refers to these regions as '*roughly* localized to amino acids 231-238' and '*roughly*

localized to amino acids 310-331' [Emphasis added]. The disclosure at lines 27-29 of page 21 of the instant specification describing the Kabat system (1991) of amino acid position numbering is limited to the numbering used with specific reference to the various hBR96 antibodies. However, in order for one to locate these specific amino acids in a generic immunoglobulin, including a non-hBR96 immunoglobulin such as an IgE, IgD, IgA, IgM etc. (all of which are currently encompassed within the scope of the claims), one has to know how to number the amino acids within the CH_2 domain and where exactly the numbering of amino acids starts within a specific sequence. This is particularly important in view of the disclosure at lines 10 and 11 of page 10 of the instant specification which vaguely refers to these regions as 'roughly localized to amino acids 231-238' and 'roughly localized to amino acids 310-331'. How one should roughly localize amino acids 231-238 and 310-331 in generic immunoglobulins belonging to different classes, subclasses or isotypes is not clear. Whether or not this represents random numbering, or whether the numbering is according to any one of several specific numbering systems known in the art, is unclear. The art recognizes multiple numbering systems, other than the Kabat system, for example, the Clothia system, the MacCallum system, the AbM system etc. See the attachment entitled 'Antibodies: general information', which also states that changes are made periodically to the same numbering system, for example, the Clothia system (see page 3 of the Attachment). The art also establishes that amino acids 231-447 numbered according to the Kabat system do *not* correspond to amino acids 231-247 of the SEQ ID number of a specific human IgG1 Fc region, but instead corresponds to amino acids 16-232 as numbered in SEQ ID NO: 11. See Figure 1 and section [0038] of Stavenhagen *et al.* (US 20060134709). The instant claims neither include the recitation of a SEQ ID number for the recited CH_2 domain, nor the recitation of a specific numbering system, rendering the metes and bounds of the claims indeterminate. The rejection stands.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Lack of Enablement)

16) Claim 1-6, 8-22 and 28-31 are rejected under 35 U.S.C § 112, first paragraph, as based on a disclosure which is not enabling. The amino acid numbering system as recited at the end of page 21 of the instant specification is critical or essential to the practice of the invention, but is not included in the claim(s) and therefore the claimed invention is not enabled by the disclosure. *In re Mahew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The specific amino acid numbering system that is used in the instant specification to number the amino acids 231-238 and amino acids 310-331 of the CH_2 domain of the constant region of the generic immunoglobulin recited in claims 1-6 and those dependent therefrom, or of the IgG1 immunoglobulin recited in claims 53-64 is critical or essential to the practice of the invention since the claims do not identify the recited CH_2 domain by a specific SEQ ID number. This is critically important because the claims lack the recitation of a SEQ ID number, and the disclosure at lines 10 and 11 of page 10 of the instant specification vaguely refers to these regions as '*roughly* localized to amino acids 231-238' and '*roughly* localized to amino acids 310-331' [Emphasis added]. The disclosure at lines 27-29 of page 21 of the instant specification describing the Kabat system (1991) of amino acid position numbering is limited to the numbering used specifically with the various hBR96 antibodies. The numbering indicated in the second part of Figure 26 is specifically pertinent to the constant region of human IgG1 and corresponds to the positions in the specific SEQ ID number depicted therein. However, the immunoglobulin recited in claims 1-22, 28-31 and 55 encompasses any generic immunoglobulin, including a non-hBR96 immunoglobulin such as IgE, IgD, IgA, IgM etc. In order for one to locate the specifically recited amino acids 231-238 and 310-331 in the CH_2 domain of a generic immunoglobulin, including a non-hBR96 immunoglobulin such as IgE, IgD, IgA, IgM etc., one has to know how to number the amino acids within the CH_2 domain of an immunoglobulin of each specific class and where exactly the numbering of amino acids starts within the domain, given the lack of identification of the recited CH_2 domain in the claims. Again, this is particularly important in view of the disclosure at lines 10 and 11 of page 10 of the instant specification which vaguely refers to these regions as 'roughly localized to amino acids 231-238' and 'roughly localized to amino acids 310-331'. How one should roughly localize amino acids 231-238 and 310-331 in generic immunoglobulins belonging to different classes, subclasses or isotypes, given the lack of identification of the recited CH_2 domain in the claims, is not understood. Whether or not amino acids 231-238 and 310-331 represent random numbering, or whether the numbering is in accordance with any one of several specific numbering systems known in the art, is unclear. The art recognizes the Kabat system and several other numbering systems other than the Kabat system, for example, the Clothia system, the MacCallum system, the AbM system etc. See the attachment entitled 'Antibodies: general information', which additionally states that changes are made periodically to the same numbering system, for example, the

Clothia system. The art further establishes that amino acids 231-447 numbered according to the Kabat system do *not* correspond to amino acids 231-247 of the SEQ ID number of a specific human IgG1 Fc region, but instead corresponds to amino acids 16-232 as numbered in SEQ ID NO: 11. See Figure 1 and section [0038] of Stavenhagen *et al.* (US 20060134709). Currently, the instant claims neither include the recitation of a SEQ ID number for the recited CH_2 domain of the recited immunoglobulin, nor the recitation of a specific numbering system. The limitations from the instant specification that are critical or essential to the practice of the invention are not included in the claim(s). The claims do not meet the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

17) Claims 53-64 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 53-64 are drawn to a method for inhibiting immunoglobulin-induced toxicity or gastrointestinal toxicity in a subject comprising administering to said subject modified BR96, ChiBR96, or a fusion protein thereof, or hBR96-2B, hBR96-2C, hBR96-2D, hBR96-2E, hBR96-2F, hBR96-2G, or hBR96-2H. Applicants state that these new claims are supported by the specification and the original claims. However, the original claims, for example, claim 35, is supportive of a method for inhibiting 'BR96 (ATCC: HB10036) induced toxicity resulting from immunoglobulin immunotherapy' in a subject comprising administering a modified BR96 as recited, but not of the method for inhibiting a generic immunoglobulin-induced toxicity as claimed in claims 53-54. Therefore, the method now claimed in the instant claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or to point to specific pages and line numbers in the originally filed specification where support for the now claimed method can be found. Applicants should specifically point out the support for any

amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection under 35 U.S.C § 112, First Paragraph (Lack of Scope of Enablement)

18) Claims 1-6, 8-22, 28-31 and 53-64 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for a method of administering to a normal dog hBR96-2B having alanine substituted at amino acid positions 235 and 237 of the CH_2 domain of chimeric BR96 produced by the HB 10460 hybridoma deposited at the ATCC, or the CH_2 domain-deleted BR96, cBR96-A, is not reasonably enabling for a method for 'inhibiting immunoglobulin-induced toxicity in a subject', or a method for 'inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject' comprising administering to said subject, via any route, a generic modified immunoglobulin (including IgG, IgM, IgA, and IgE) containing structurally altered multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The method claimed in the instant claims 1-22 and 28-31 is a method 'for inhibiting immunoglobulin-induced toxicity in a subject' comprising administering to said subject an immunoglobulin that is modified as recited. The method claimed in claims 53-57 is a method 'for inhibiting immunoglobulin-induced gastrointestinal toxicity in a subject' comprising administering an immunoglobulin that is modified as recited to said subject. This requires that the subject to whom the modified immunoglobulin is administered has toxicity pre-induced by an immunoglobulin that is

unmodified in the multiple toxicity-associated regions, which immunoglobulin was administered to the subject prior to the administration of the modified immunoglobulin having structural alteration(s) in the CH2 domain, as recited. However, a review of the instant specification indicates the following. The *in vivo* demonstration in Example 3 is limited to a showing that a set of dogs which 'received', or which were 'treated with' 400 mg/m^2 of CH2 domain-containing chimeric BR96 antibody experienced the typical gastrointestinal toxicity, whereas another set of dogs which 'received' 400 mg/m^2 of the CH_2 domain-deleted chimeric BR96 antibody, cBR96-A, displayed no GI toxicity. This example describes a mere administration of a CH_2 domain-deleted chimeric BR96 antibody to dogs and does not provide enablement for the instantly claimed method, because the now claimed method requires that the recited subject has a generic toxicity or gastrointestinal toxicity pre-induced by a normal or CH2-domain-unmodified immunoglobulin and is required to inhibit such immunoglobulin-induced toxicity or gastrointestinal toxicity in said subject having the toxicity or gastrointestinal toxicity. Furthermore, the specification does not describe what is encompassed in the term 'receiving' and 'treated with'. Whether or not the term 'receiving' or 'treated with', as recited in the paragraph bridging pages 36 and 37 and second full paragraph of page 37 of the specification, includes oral administration or local delivery to the GI tract of the modified immunoglobulin, or whether it includes non-oral or non-local administration, including parenteral administration, is not specifically described.

The last paragraph on page 37 of the specification describes 'Toxicology study of hBR96-2B' and states that a dose of 400 mg/m^2 of one single species of BR96, that is structurally altered specifically at amino acid residues 235 and 237 in the CH_2 domain of the constant region of said BR96, did not cause hematemesis or blood stools in high Lewis Y expressor dogs, whereas chimeric BR96 causes hemorrhagic lesions and mucosal erosions in a separate set of dogs. Again, this does not provide enablement for the instantly claimed method for 'inhibiting immunoglobulin-induced' generic toxicity or gastrointestinal toxicity in a generic subject or a mammalian subject. Example 3 and the last paragraph of page 37 of the instant specification merely demonstrate how to avoid inducing toxicity mediated by effector functions of the Fc receptor or complement-mediated toxicity in dogs by not 'treating' the dogs with a chimeric BR96, but treating with a CH_2 domain-deleted chimeric BR96 antibody, or hBR96-2B that is structurally altered specifically at amino acid residues 235 and 237 in the CH_2 domain of the constant region of BR96. Furthermore, as per the precise definition provided at

lines 8-15 of page 10 of the instant specification for the term 'multiple toxicity associated domains', hBR96-2B having a specific amino acid substitution at amino acid residues 235 and 237 does not qualify as an immunoglobulin modified in the multiple toxicity associated domains or regions of the CH_2 domain of the constant region. See also first full paragraph on page 3 of Applicants' Appeal Brief; and also lines 21 and 22 on page 4 of the specification.

Therefore, the instant specification is enabling for a method of administering to a normal dog hBR96-2B having alanine at amino acid positions 235 and 237 of the CH_2 domain of chimeric BR96 produced by the HB 10460 hybridoma deposited at the ATCC, or the CH_2 domain-deleted BR96, cBR96-A, is not reasonably enabling for a method for 'inhibiting immunoglobulin-induced toxicity in a subject', or a method for 'inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject' comprising administering to said subject, via any route, a generic modified immunoglobulin (including IgG, IgM, IgA, and IgE) containing structurally altered multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain. The mere administration, to a non-canine subject, such as monkeys, mice, or humans, of a CH_2 domain-deleted (i.e., structurally altered) IgG1 antibody, such as chimeric CC49 monoclonal antibody, or $F(ab')_2$ BR96 fragment, i.e., BR96 immunoglobulin structurally altered such that it does not contain amino acids 231-238 and amino acids 310-331 of the CH_2 domain of the constant region due to deletion of the CH_2 domain, was known in the art at the time of the invention. See the teachings below of Slavin-Chiorini *et al.* (*Cancer Res.* 55: 5957s-5967s, 01 December 1995) and Hellstrom *et al.* (US 6,020,145). Therefore, a method of administration of such a CH2-deleted antibody to a non-canine subject is enabled. However, a similar disclosure from the instant specification wherein a CH2-deleted antibody is administered to a subject, or the teachings from the prior art wherein a CH2-deleted antibody is administered to a mammalian subject, does not provide enablement for the instantly claimed method for 'inhibiting immunoglobulin-induced toxicity in a subject comprising administering to said subject' the altered immunoglobulin, and for the instantly claimed method for 'inhibiting immunoglobulin-induced gastrointestinal toxicity in a subject comprising administering to said subject' as recited currently. The instant claims are viewed as not meeting the scope of enablement provision of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

19) Claims 1-6, 8-22, 28-31 and 53-64 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 53, 59 and those dependent therefrom are indefinite in the limitations: 'multiple toxicity-associated regions are structurally altered by mutating amino acids 235 and 237 in said CH_2 domain', because it is unclear how structural alterations only at amino acids 235 and 237 constitute alteration of multiple toxicity-associated regions. The specification specifically defines the "multiple toxicity associated domains" as meaning more than one discrete toxicity associated domain, i.e., at least two toxicity associated domains in the immunoglobulin molecule, one roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331, an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues in *both of these domains*. It is unclear how antibodies structurally altered by mutating only amino acids 235 and 237 in the CH_2 domain qualify as antibodies having alterations **both** in a toxicity associated domain in the C-terminal region of the CH2 domain (roughly localized to amino acids 310-331) **as well as** alterations in a toxicity associated domain in the N-terminal region of the CH2 domain (roughly localized to amino acids 231-238). Doesn't the definition specifically exclude structural alterations targeting a single toxicity associated domain, i.e., structural alterations only in the region of amino acids 231-238 or structural alterations only in the region of amino acids 310-331 of CH_2 domain? See lines 8-15 on page 10 of the instant specification and paragraph 14 above.

(b) Claims 54-58 and 60-64 are indefinite and confusing because it is unclear how a gastrointestinal toxicity induced in a mammalian subject by any generic immunoglobulin or any IgG1 can be inhibited by administering to said subject the specific heterologous BR96 (HB 10036), ChiBR96 (HB 10460) or a fusion protein thereof, or HBR96-2B, HBR96-2C, HBR96-2D, HBR96-2E, HBR96-2F, HBR96-2G, or HBR96-2H. Does it mean that the gastrointestinal toxicity caused for example by an anti-HIV antibody in a subject can be inhibited by administration of the heterologous modified BR96 (HB 10036), ChiBR96 (HB 10460) or a fusion protein thereof, or HBR96-2B,

HBR96-2C, HBR96-2D, HBR96-2E, HBR96-2F, HBR96-2G, or HBR96-2H? Clarification is requested.

(c) Claims 1-22 and 28-31 are indefinite and confusing in that the claimed method for inhibiting 'immunoglobulin-induced toxicity in a subject' includes the single step of administering to said subject a modified immunoglobulin as recited. It is unclear how administration of a modified generic immunoglobulin to a subject having toxicity induced (i.e., preinduced) by an immunoglobulin specific to a disease target can inhibit the toxicity? Does it mean that the toxicity caused for example by an anti-HIV antibody in a subject can be inhibited by administration of a heterologous modified immunoglobulin, for example, modified BR96? Clarification is requested.

Rejection(s) under 35 U.S.C § 102

20) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in-
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

21) Claims 1, 2, 5, 8, 28, 29, 53, 59 and 63 are rejected under 35 U.S.C § 102(a) as being anticipated by Slavin-Chiorini *et al.* (*Cancer Res.* 55: 5957s-5967s, 01 December 1995) as evidenced by Carlin *et al.* (*J. Nucl. Med.* 44: 1827-1838, 2003, abstract) and Cook *et al.* (*Cancer Biother. Radiopharm.* 11: 415-422, 1996, abstract).

The recitation 'for inhibiting immunoglobulin-induced ... toxicity' has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

It is noted that the only active step of the claimed method that is required to be met by the prior art is the step of administering to a mammalian subject a structurally altered antibody or IgG1

antibody comprising a variable region and a constant region, wherein multiple-toxicity associated regions in the CH_2 domain of the constant region are modified so as to render the constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement. As defined at lines 24 and 25 of page 10 of the specification, deletion qualifies as a structural alteration.

Slavin-Chiorini *et al.* taught a method of administering to rhesus monkeys (i.e., mammalian subjects) a CH_2 domain-deleted (i.e., structurally altered) chimeric CC49 monoclonal antibody (i.e., IgG1). The CH_2 domain-deletion of the constant region of the prior art chimeric CC49 monoclonal antibody constitutes structural alteration of multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, since these amino acids are altered via deletion. Slavin-Chiorini *et al.* taught selecting the CC49 immunoglobulin which binds a tumor-associated TAG-72 target, mutating said immunoglobulin by CH_2 domain deletion which results in the deletion of the multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, and administering the altered immunoglobulin to the mammalian subject. The CH_2 domain-deleted CC49 immunoglobulin of the prior art is conjugated to ^{131}-iodide (i.e., a cytotoxic agent). See abstract; page 5958s; Materials and Methods; Results; and second full paragraph in right column on page 5959s. The prior art method of administering to rhesus monkeys a CH_2 domain-deleted chimeric CC49 monoclonal IgG1 antibody necessarily serves as the instantly claimed method for inhibiting immunoglobulin-induced toxicity including gastrointestinal toxicity in a subject or a mammalian subject since the single administration step recited in the claims is met by the prior art method. Since the prior art method step and the instantly recited method step are identical, the prior art method necessarily serves as the claimed method for inhibiting immunoglobulin-induced toxicity including gastrointestinal toxicity in a subject or a mammalian subject. The prior art CH_2 domain-deleted chimeric CC49 monoclonal IgG1 antibody is viewed as inherently comprising a variable region and a constant region absent evidence to the contrary.

That the prior art ^{131}-iodide serves as an intrinsic cytotoxic agent is inherent from the teachings of Slavin-Chiorini *et al.* in light of what is known in the art. For instance, Carlin *et al.* describe ^{131}-iodide to be a cytotoxic agent (see abstract of Carlin *et al.*). Similarly, that the prior art CC49 monoclonal antibody is an IgG1 antibody is also inherent from the teachings of Slavin-Chiorini *et al.* in light of what is known in the art. For instance, Cook *et al.* describe the CC49 monoclonal

antibody to be an IgG1 antibody (see abstract of Cook *et al.*).

The teachings of Slavin-Chiorini *et al.* anticipate the instant claims. Carlin *et al.* or Cook *et al.* is **not** used as a secondary reference in combination with Slavin-Chiorini *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Slavin-Chiorini *et al.* with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978).

22) Claims 1-6, 8, 11, 13-15, 17-19, 21, 22, 28-31, 53, 55-59 and 61-63 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Hellstrom *et al.* (US 6,020,145).

Hellstrom *et al.* taught a method of administering to mice $F(ab')_2$ BR96 fragment (i.e., BR96 immunoglobulin structurally altered such that it does not contain CH_2 domain of the constant region). The BR96 immunoglobulin or its $F(ab')_2$ fragment specifically recognizes and binds a tumor target or Lewis Y. Hellstrom *et al.* taught a method of administering to a subject including a human subject an effective amount of a composition comprising said BR96 $F(ab')_2$ fragment, chimeric BR96 $F(ab')_2$ fragment alone, or being conjugated to a cytotoxin or chemotherapeutic agent, i.e., BR96 $F(ab')_2$-lysPE40 or chimeric BR96 $F(ab')_2$-lysPE40 (i.e., Ig fusion protein). Hellstrom *et al.* taught selecting the BR96 or chimeric BR96 immunoglobulin which binds a tumor-associated target, altering said immunoglobulin to produce BR96 $F(ab')_2$ fragment, chimeric BR96 $F(ab')_2$ fragment, BR96 $F(ab')_2$-lysPE40 or chimeric BR96 $F(ab')_2$-lysPE40, and administering the altered immunoglobulin or the Ig fusion protein to the mammalian subject. Hellstrom's BR96 monoclonal is produced by the hybridoma deposited at the ATCC as HB 10036. Hellstrom's chimeric BR96 is produced by the hybridoma deposited at the ATCC as HB 10460. Hellstrom's chimeric BR96 contains human IgGγ1 heavy chain. The CH_2 domain-deletion of the constant region of the prior art BR96 $F(ab')_2$ fragment or chimeric BR96 $F(ab')_2$ fragment constitutes structural alteration of multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, since these amino acids are altered via deletion. See Examples 11, 8 and 7; last paragraph of column 66; abstract; paragraph bridging columns 74 and 75; columns 47 and 48; Table in column 31; lines 45 and 46 and last paragraph in column 16; third paragraph in column 15; columns 16 and 17; column 19; and lines 52-60 in column 13. The prior art method of administering to mice or a human a CH_2 domain-deleted

$F(ab')_2$ fragment of BR96 (HB 10036) or ChiBR96 antibody (HB 10460) necessarily serves as the instantly claimed method for inhibiting immunoglobulin-induced toxicity including gastrointestinal toxicity in a subject or a mammalian subject since the single administration step recited in the claims is met by the prior art method. Since the prior art method step and the instantly recited method step are identical, and since the prior art modified immunoglobulin and the prior art modified immunoglobulin are identical, the prior art method necessarily serves as the claimed method for inhibiting immunoglobulin-induced toxicity, including gastrointestinal toxicity, in a subject or a mammalian subject. The prior art chimeric BR96 $F(ab')_2$ fragment, BR96 $F(ab')_2$-lysPE40 or chimeric BR96 $F(ab')_2$-lysPE40 is viewed as inherently comprising a variable region and a constant region absent evidence to the contrary.

Claims 1-6, 8, 11, 13-15, 17-19, 21, 22, 28-31, 53, 55-59 and 61-63 are anticipated by Hellstrom *et al.*

23) Claims 1, 5, 12, 16 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gundel *et al.* (WO 93/02702, already of record).

Gundel *et al.* taught a method of administering to an asthma patient F(ab)2 fragments of an antibody that binds to Lewis X antigen-containing ELAM-1 receptor (see claims 1-3 and 8-11; last half of page 7 and 6). Gundel's F(ab)2 antibody fragment is viewed as a structurally altered immunoglobulin having CH_2 domain-deletion of the constant region which CH_2 domain deletion constitutes structural alteration of multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, since these amino acids are altered via deletion. Since the prior art method step and the instantly recited method step are identical, and since the prior art modified immunoglobulin and the prior art modified immunoglobulin are identical, the prior art method necessarily serves as the claimed method for inhibiting immunoglobulin-induced toxicity in a mammalian subject. The prior art Lewis X antigen-binding F(ab)2 is viewed as inherently comprising a variable region and a constant region absent evidence to the contrary.

Claims 1, 5, 12, 16 and 20 are anticipated by Gundel *et al.*

Remarks

24) Claims 1-6, 8-22, 28-31 and 53-64 stand rejected.

25) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number, (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

26) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

August, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER

Antibodies: general information

Visitors since 9th November, 2000

New! Test the 'humanness' of your antibody. Our new server lets you compare your sequence with all human sequences to obtain a similarity score and compare it with a distribution of human and mouse sequences.

Visit the page of information and links to accompany my book chapter *Protein Sequence and Structure Analysis of Antibody Variable Domains.* In: **Antibody Engineering Lab Manual** (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). [Information] [Purchase]

- The Kabat Numbering Scheme
- The Chothia Numbering Scheme
- Table of CDR Definitions
- How to identify the CDRs by looking at a sequence
- Table of mean contact data

The Kabat Numbering Scheme

The Kabat numbering scheme is a **widely adopted standard** for numbering the residues in an antibody in a consistent manner. However the scheme **has problems!**

First, since the numbering scheme was **developed from sequence data** (a fairly limited set), the **position at which insertions occur in CDR-L1 and CDR-H1 does not match the structural insertion position**. Thus topologically equivalent residues in these loops do not get the same number.

Second, the numbering adopts a **rigid specification**. For example in the potentially very long CDR-H3, insertions are numbered between residue H100 and H101 with letters up to K (i.e. H100, H100A ... H100K, H101). If there are more residues than that, there is no standard way of numbering them. Such situations occur at other positions too.

The numbering throughout the chains is as follows:

Light chain

0	1	2	3	4	5	6	7	8	9
10	11	12	13	14	15	16	17	18	19
20	21	22	23	24	25	26	27		
27A	27B	27C	27D	27E	27F			28	29
30	31	32	33	34	35	36	37	38	39
40	41	42	43	44	45	46	47	48	49
50	51	52	53	54	55	56	57	58	59
60	61	62	63	64	65	66	67	68	69
70	71	72	73	74	75	76	77	78	79
80	81	82	83	84	85	86	87	88	89
90	91	92	93	94	95				
95A	95B	95C	95D	95E	95F	96	97	98	99
100	101	102	103	104	105	106			
106A							107	108	109

Heavy chain

0	1	2	3	4	5	6	7	8	9
10	11	12	13	14	15	16	17	18	19
20	21	22	23	24	25	26	27	28	29
30	31	32	33	34	35				
35A	35B					36	37	38	39
40	41	42	43	44	45	46	47	48	49
50	51	52							
52A	52B	52C	53	54	55	56	57	58	59
60	61	62	63	64	65	66	67	68	69
70	71	72	73	74	75	76	77	78	79
80	81	82							
82A	82B	82C	83	84	85	86	87	88	89
90	91	92	93	94	95	96	97	98	99
100									
100A	100B	100C	100D	100E	100F	100G	100H	100I	100J
100K	101	102	103	104	105	106	107	108	109
110	111	112	113						

The Chothia Numbering Scheme

The Chothia numbering scheme is identical to the Kabat scheme, but places the **insertions in CDR-L1 and CDR-H1 at the structurally correct positions**. This means that topologically equivalent residues in these loops do get the same label (unlike the Kabat scheme).

There are **two disadvantages**: **first**, the **Kabat scheme is so widely used** that some confusion can arise; **second**, Chothia *et al.* **changed** their numbering scheme as of their 1989 Nature paper such that insertions in CDR-L1 are placed after residue L31 rather than L30. Examining the conformations of the loops shows that **L30 is the correct position.**

Note That in their latest paper (Al-Lazikani *et al.*, (1997) JMB **273**,927-948), Chothia's group returns to using residue L30 as the insertion site in CDR-L1!

The pre-1989/post-1997 Chothia numbering (the structurally correct version) throughout the chains follows.

Light chain

0	1	2	3	4	5	6	7	8	9
10	11	12	13	14	15	16	17	18	19
20	21	22	23	24	25	26	27	28	29
30									
30A	30B	30C	30D	30E	30F				
	31	32	33	34	35	36	37	38	39
40	41	42	43	44	45	46	47	48	49
50	51	52	53	54	55	56	57	58	59
60	61	62	63	64	65	66	67	68	69
70	71	72	73	74	75	76	77	78	79
80	81	82	83	84	85	86	87	88	89
90	91	92	93	94	95				
95A	95B	95C	95D	95E	95F	96	97	98	99
100	101	102	103	104	105	106			
106A							107	108	109

Heavy chain

0	1	2	3	4	5	6	7	8	9
10	11	12	13	14	15	16	17	18	19
20	21	22	23	24	25	26	27	28	29
30	31								
31A	31B								
		32	33	34	35	36	37	38	39
40	41	42	43	44	45	46	47	48	49
50	51	52							
52A	52B	52C	53	54	55	56	57	58	59
60	61	62	63	64	65	66	67	68	69
70	71	72	73	74	75	76	77	78	79
80	81	82							
82A	82B	82C	83	84	85	86	87	88	89
90	91	92	93	94	95	96	97	98	99
100									
100A	100B	100C	100D	100E	100F	100G	100H	100I	100J
100K	101	102	103	104	105	106	107	108	109
110	111	112	113						

Table of CDR Definitions

A number of definitions of the CDRs are commonly in use:

- **The Kabat definition** is based on sequence variability and is the most commonly used
- **The Chothia definition** is based on the location of the structural loop regions
- **The AbM definition** is a compromise between the two used by Oxford Molecular's *AbM* antibody modelling software
- **The contact definition** has been recently introduced by us and is based on an analysis of the available complex crystal structures. This definition is likely to be the most useful for people wishing to perform mutagenesis to modify the afinity of an antibody since these are residues which take part in interactions with antigen. Lists of CDR residues making contact in each antibody with summary data for each CDR

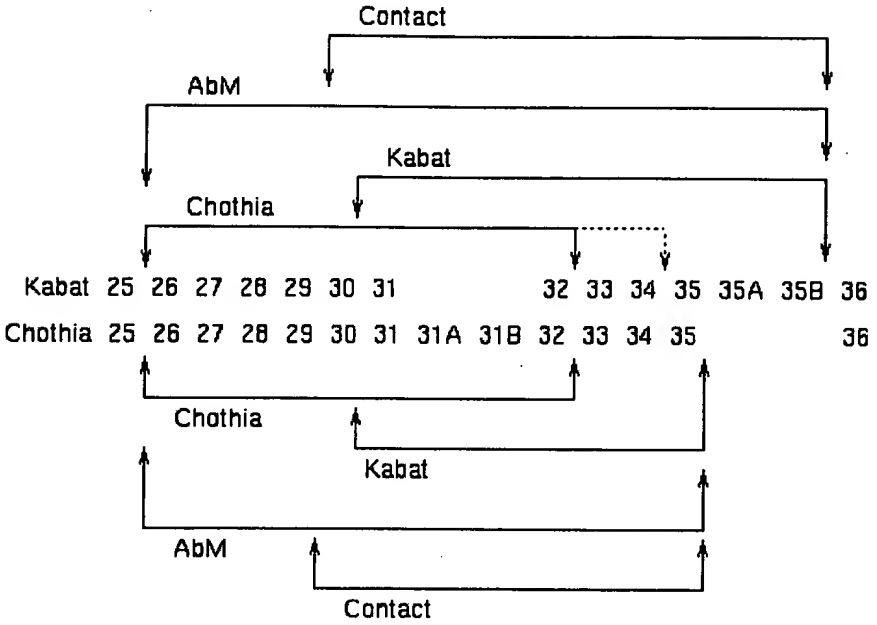
Note that some of these definitions vary depending on the indiviual publication examined.

Loop	Kabat	AbM	Chothia	Contact
L1	L24--L34	L24--L34	L24--L34	L30--L36
L2	L50--L56	L50--L56	L50--L56	L46--L55
L3	L89--L97	L89--L97	L89--L97	L89--L96
H1	H31--H35B (Kabat Numbering)	H26--H35B	H26--H32..34	H30--H35B
H1	H31--H35 (Chothia Numbering)	H26--H35	H26--H32	H30--H35
H2	H50--H65	H50--H58	H52--H56	H47--H58
H3	H95--H102	H95--H102	H95--H102	H93--H101

Note that the end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop. (This is because the Kabat numbering scheme places the insertions at H35A and H35B.)

- If neither H35A nor H35B is present, the loop ends at H32
- If only H35A is present, the loop ends at H33

- If both H35A and H35B are present, the loop ends at H34



This diagram illustrates the alternative definitions for CDR-H1. The Kabat and Chothia numbering schemes are shown horizontally and the Kabat, Chothia, AbM and Contact definitions of the CDRs are shown with arrows above and below the two numbering schemes.

How to identify the CDRs by looking at a sequence

The following set of rules will allow you to find the CDRs in an antibody sequence. **Note** that the word 'always' should always be treated with care! There are rare examples where these virtually constant features do not occur (for example the human heavy chain sequence EU does not have Trp-Gly after CDR-H3). The Cys residues are the best conserved feature.

CDR-L1

Start	Approx residue 24
Residue before	**always** a Cys
Residue after	**always** a Trp. Typically Trp-Tyr-Gln, but also, Trp-Leu-Gln, Trp-Phe-Gln, Trp-Tyr-Leu
Length	10 to 17 residues

CDR-L2

Start	**always** 16 residues after the end of L1
Residues before	generally Ile-Tyr, but also, Val-Tyr, Ile-Lys, Ile-Phe
Length	**always** 7 residues (except NEW (7FAB) which has a deletion in this region)

CDR-L3

Start	**always** 33 residues after end of L2 (except NEW (7FAB) which has the deletion at the end of CDR-L2)
Residue before	**always** Cys
Residues after	**always** Phe-Gly-XXX-Gly
Length	7 to 11 residues

CDR-H1

Start	Approx residue 26 (**always** 4 after a Cys) [Chothia / AbM defintion]; Kabat definition starts 5 residues later
Residues before	**always** Cys-XXX-XXX-XXX
Residues after	**always** a Trp. Typically Trp-Val, but also, Trp-Ile, Trp-Ala
Length	10 to 12 residues [AbM definition]; Chothia definition excludes the last 4 residues

CDR-H2

Start	**always** 15 residues after the end of Kabat / AbM definition) of CDR-H1
Residues before	typically Leu-Glu-Trp-Ile-Gly, but a number of variations
Residues after	Lys/Arg-Leu/Ile/Val/Phe/Thr/Ala-Thr/Ser/Ile/Ala
Length	Kabat definition 16 to 19 residues; AbM (and recent Chothia) definition ends 7 residues earlier

CDR-H3

Start	**always** 33 residues after end of CDR-H2 (**always** 2 after a Cys)

Residues before **always** Cys-XXX-XXX (typically Cys-Ala-Arg)
Residues after **always** Trp-Gly-XXX-Gly
Length 3 to 25(!) residues

Table of mean contact data

Following an analysis of the contacts between antibody and antigen in the complex structures available in the Protein Databank, we have generated a set of mean contact data. The full method by which these results were obtained is described in the following paper: MacCallum, R. M., Martin, A. C. R. and Thornton, J. T. **Antibody-antigen interactions: Contact analysis and binding site topography.** *J. Mol. Biol.* **262**, 732-745.

Briefly, we have analysed the number of contacts made at each position, defining contact as burial by > 1 square Angstrom change in solvent accessibility. These data give a simple measure of how likely a residue is to be involved in antigen contact.

Second, we have calculated the mean percentage burial over the accessible residues.

Click here for an image showing a composite combining site containing all CDR conformations coloured by contact propensity.

The table presents the chain name, residue number (N.B. This is **pre-1989 Chothia Numbering**), the number of contacts and the mean percent burial. The data are available by clicking here.

An alternative simplified view is presented as a list of CDR residues making contact in each antibody with summary data for each CDR.

Last Modified: 14-Jun-2006